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Patricia McNeal

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Medical Monitoring:

The acute and chronic exposures of the Tie Plant area residents to markedly elevated levels of multiple toxic emissions from the Koppers plant for decades place them at increased risk for significant adverse health effects in the future. Those individuals with already diagnosed exposure-related medical conditions or diseases are certain to need comprehensive medical care for the remainder of their lives. A medical monitoring program, including the components described below, allows for the early detection of disease. This monitoring regime is considerably different from that recommended for normal healthy adults or children with no known toxic exposures. Additionally, a monitoring regime is reasonably necessary and indicated for an exposed group of individuals, such as the Tie Plant area residents, according to modern standards of occupational and environmental medicine.

1. Complete history (baseline) – medical, occupational, and environmental.

2. Complete (baseline) physical examination – to include:

   breast examination (yearly beginning at age 18),

   testicular examination (yearly beginning at age 14)

   pelvic examination with pap smear (yearly beginning at age 18)

   rectal examination (yearly beginning at age 30)

3. Interim history and physical – once per year or more often as indicated by symptoms or signs of disease and/or on the basis of clinical evaluation.

4. Oral/dental examination – once every 6 months or more often as indicated by symptoms or signs of disease.

5. Complete otolaryngology evaluation including assessment for chemosensory disorders (smell and taste) – once per year or more often as indicated by symptoms or signs of disease.

6. Complete neuropsychological evaluation – initial and once every 2 years or as indicated by symptoms or test results.

7. Complete educational achievement and intellectual capacity testing for all children every 1-3 years as indicated beginning at age 2-3 until age 18, or longer if needed.

8. Complete developmental and neurological evaluation of all infants and preschool children to be repeated with neuropsychological and/or other developmental testing at intervals to be determined based on initial and subsequent assessments.

9. Baseline laboratory evaluations:

   urinalysis

urine cytology

complete blood count with differential

blood chemistries including electrolytes

liver profile

renal profile

lipid profile

thyroid function tests

urine and/or blood heavy metal testing as indicated

PCBs

dioxins and dibenzofurans

urine 1 – hydroxypyrene

specific urine and blood tests for mutagenic and carcinogenic substances

Tests to be repeated yearly except PCBs, dioxins/dibenzofurans, and tests for mutagenic and carcinogenic substances – to be repeated every 2-5 years or as indicated.

10. Baseline chest x-rays for adults repeated every 2-3 years beginning at age 40 or as indicated. Chest x-rays for those under 40 as indicated by exposure history or by signs or symptoms of disease.

11. Mammography – baseline at age 30 (or earlier based on family and/or exposure history; once every 2 years ages 30-40; once per year after age 40. Schedule may vary depending on risk factors.

12. Stool for occult blood yearly beginning at age 30.

13. Flexible sigmoidoscopy – baseline at age 40; then every 2-3 years or as indicated.

14. Spirometry and peak flow meter reading – baseline followed by yearly testing. More frequent testing to be performed on individuals with symptoms or signs of respiratory disease (e.g. asthma, RADS, etc.). Oximetry as indicated.

15. Electrodiagnostic testing – initial EMG and nerve conduction studies – repeat as indicated.

16. CAT Scan and/or MRI of brain with or without contrast as indicated.

17. Other appropriate laboratory testing as indicated, including but not limited to: sedimentation rate, PSA, sputum cytology, thyroid function testing, immunologic testing, sperm count, fertility evaluation, fetal in utero or amniotic fluid testing, non-routine blood chemistry evaluations, fat biopsy, CEA.

18. Other appropriate diagnostic studies as indicated, including but not limited to: abdominal and/or pelvic sonography, abdominal and/or pelvic CT and/or MRI studies, and PET scans of the brain.

19. Genetic and reproductive counseling and evaluation.

20. Helical CT of the chest and abdomen is necessary for all Exposed Plaintiffs over the age of 35 at approximately 3-year intervals. Virtual colonoscopy should be part of the helical CT study to enhance detection of lower gastrointestinal tract cancer (Cost $1500). This test will detect cancer as small as 2 millimeters in diameter. At this tumor size and stage it is most likely that a cure can be achieved for most malignancies. Cancer of the lymph nodes, kidney, thyroid, lung, colon, pancreas, liver and other locations can be detected with this test. If a non-calcified nodule is seen, follow-up is required, including biopsy or other procedures.

The following costs are based on fee schedules from Syracuse, New York, or on estimated costs for services for which a specific fee has not been determined. This list includes diagnostic tests which are currently indicated or may be necessary and is not meant to be all inclusive.

MEDICAL SURVEILLANCE COSTS

Test Description	**Frequency / Age**	**Estimated Cost Per Visit, Test, or Procedure**
Initial History & Physical (H&P)	Initial	350.00
Breast Physical Exam	1/year begin at 18	(included in H&P)
Testicular Physical Exam	1/year begin at 14	(included in H&P)
Oral/Dental Exam	1/year or as indicated	90.00
Interim H & P	1/year or as indicated by symptoms	250.00
Rectal Exam	1/year begin at 30	(included in H&P)
Pelvic Exam with PAP smear	1/year begin at 18	175.00
Otolaryngology (ENT) Eval.	Initial and 1/year or as indicated	250.00
(Cost does not include anosmia evaluation - Initial and follow up as indicated)		
Neuropsychological Eval.	Initial and every 2 years or as indicated by symptoms	2,400.00
Sputum Cytology	1/year begin at 30 (earlier as indicated)	85.00
Chest X-Ray	Initial at 40, then every 2-3 years or as indicated by symptoms	90.00
Mammography	Baseline (30) and per schedule above	155.00
Stool Occult Blood	1/year begin at 30	20.00
Urinalysis	1/year	15.00
Urine Cytology	1/year begin at 25 (earlier as indicated)	45.00
Prostate Specific Antigen	1/year begin at 40 (earlier as indicated)	50.00
Blood Chemistry (Comprehensive Metabolic Profile)	1/year	50.00
Complete Blood Count	1/year	30.00
Liver Profile	1/year	45.00
Sedimentation Rate	As indicated	18.00
EKG	Initial at 40 and every 3	85.00

	years after 40	
Spirometry	Initial, then yearly (more often as indicated)	85.00
Spirometry - Pre & Post Bronchodilator	As indicated	130.00
Peak Flow Meter	Initial, then yearly (more often as indicated)	50.00
Flexible Sigmoidoscopy	Initial at 40, then every 2-3 years or as indicated	225.00
MRI (Brain) w/o contrast	Frequency as indicated by clinical condition	500.00
MRI (Brain) w/ contrast	" "	500.00
MRI (Brain) w/o contrast followed by contrast	" "	1,000.00
CAT Scan (Brain) w/ contrast	" "	453.00
CAT Scan (Brain) w/o contrast	" "	370.00
CAT Scan (Brain) w/o contrast followed by contrast	" "	554.00
EMG & Nerve Conduction Studies 1 Extremity	" "	175.00
EMG & Nerve Conduction Studies 2 Extremities	" "	245.00
EMG & Nerve Conduction Studies 3 Extremities	" "	310.00
EMG & Nerve Conduction Studies 4 Extremities	" "	375.00
EMG & Nerve Conduction Studies Cranial Nerve - Unilateral	" "	150.00
EMG & Nerve Conduction Studies Cranial Nerve - Bilateral	" "	240.00
EMG & Nerve Conduction Studies Limited Studies of Specific Muscles	" "	70.00
EMG & Nerve Conduction Studies Single Fiber, Any Technique	" "	135.00
EMG & Nerve Conduction Studies Per Nerve for Each Motor Nerve	" "	75.00

EMG & Nerve Conduction Studies Per Nerve for Each Sensory Nerve	" "	65.00
Helical CT of chest and abdomen	Initial, then every 3 years	1500.00

The medical surveillance protocol above (including, but not limited to, the diagnostic tests specified) is necessary, with a reasonable degree of medical certainty, to mitigate the risk of adverse health effects which individuals have suffered or may incur as a result of their exposures to toxic contaminants released from the Grenada, Mississippi, Koppers plant. This protocol may be supplemented or amended in the future, based on receipt of additional information.

Appendix A: EXCERPT FROM ATSDR DIOXIN

The following is a quote that contains information on the reproductive and developmental effects of dioxins from the ATSDR Toxicological Profile on dioxins, Pages 291 to 299, (ATSDR 1998).

Reproductive Effects. The weaknesses of the epidemiology studies examining reproductive end points limits drawing conclusions regarding the reproductive toxicity of 2,3,7,8-TCDD in humans. Some common weaknesses include lack of exposure data (many of the studies rely on self-reported 2,3,7,8-TCDD exposure; CDC (1987) found that 2,3,7,8-TCDD blood levels of Vietnam veterans reporting direct or indirect exposure to Agent Orange were not significantly different from levels in non-Vietnam veterans), concomitant exposure to other chemicals, and lack of data on 2,3,7,8-TCDD levels at the time of conception. Several studies looked for an association between 2,3,7,8-TCDD exposure and an increased risk of spontaneous abortions, most did not find any statistically significant alterations following paternal exposure to 2,3,7,8-TCDD (Aschengrau and Monson 1989; Smith et al. 1982; Wolfe et al. 1995). An increased incidence of spontaneous abortions, was observed in women living near an herbicide manufacturing facility (Forsberg and Nordstrom 1985). However, this study has been criticized for its small sample size, inadequate discussion of sample selection, and concomitant exposure to other chemicals, including dibenzofurans (Sweeney 1994). In Vietnamese residents living in areas sprayed with Agent Orange, an increased incidence of hydatiform moles was observed (Phuong et al. 1989a). A later control study by Ha et al. (1996) did not confirm the results of the Phuong et al. (1989a) study. In the 7½-year

period after the Seveso accident, the number of female children born to parents living in area A was significantly higher than the number of male children (48 versus 26) (Mocarelli et al. 1996). An increased ratio of female to male children was also reported in workers of a 2,4,5-T production facility in Ufa, Russia (Basharova 1996) and in men exposed to chlorophenate wood preservatives contaminated with CDD (Dimich-Ward et al. 1996; James 1997). No alterations were found in the Missouri cohort of women living in 2,3,7,8-TCDD-contaminated areas (Stockbauer et al. 1988). Although several studies provide suggestive evidence of a relationship between CDD exposure and alterations in the sex ratio, the data are inadequate to establish a causal relationship. Additionally, it is not known how 2,3,7,8-TCDD affects the sex ratio. It has been postulated that the effect may be due to an alteration in hormonal balance or a disproportional number of miscarriages of male fetuses.

Data on 2,3,7,8-TCDD-induced alterations in gonads and reproductive endocrine function in humans are limited to effects observed in males. Decreased testicular size without any hormonal changes was found in Air Force Vietnam veterans exposed to 2,3,7,8-TCDD during Operation Ranch Hand (USAF 1991). This finding (decreased testicular size) was not confirmed when a more sensitive measurement device (ultrasound) was used (Henriksen et al. 1996). Wolfe et al. (1985) found no alterations in sperm count or morphology in veterans involved in Operation Ranch Hand. Henriksen et al. (1996) assessed the possible relationship between 2,3,7,8-TCDD exposure and alterations in testosterone levels, FSH, LH, testicular abnormalities, sperm abnormalities, and sperm counts in the Operation Ranch Hand cohort (reproductive parameters were assessed in

1982, 1987, and 1992) and found no consistent, statistically significant alterations. Increases in FSH and LH levels and decreases in testosterone levels were observed in males working in 2,4,5-trichlorophenol manufacturing facilities (NIOSH cohort); however the magnitude of the changes in hormone levels was small (Egeland et al. 1994). The study authors note that increases in LH levels and decreases in testosterone levels were not found in the same men, suggesting that 2,3,7,8-TCDD may result in subtle alterations rather than primary gonadal failure.

A number of reproductive effects, including decreased fertility, damage to the gonads, and alterations in hormone levels, have been observed in male and female animals orally exposed to 2,3,7,8-TCDD. In male rats, a dose- and time-dependent reduction of serum testosterone and dihydrotestosterone levels was observed after acute oral exposure to 2,3,7,8-TCDD (Mebus et al. 1987; Moore et al. 1985, 1991). Furthermore, male rats had decreased weight of seminal vesicles following oral exposure to 2,3,7,8-TCDD (Al-Bayati et al. 1988; Moore et al. 1985) and reduced spermatogenesis after oral and exposure (Al-Bayati et al. 1988; Chahoud et al. 1989; Van Miller et al. 1977). Biochemical changes in rat testes included dose- and time-dependent decreases in 17-hydroxylase activity and 20-lyase activity and reduced microsomal cytochrome P-450 (Mebus et al. 1987). Decreases in testicular superoxidase dismutase and glutathione peroxidase activities, and increases in protein kinase C activity and lipid peroxidation were also found in 2,3,7,8-TCDD-exposed rats (Al-Bayati et al. 1988). On the basis of the above data, it was postulated that the androgen deficiency is due to decreased androgen synthesis. It was further suggested that the morphological changes in rat testes

may be due to changes in lipid peroxidation. Pre- and/or postimplantation losses have been observed in rats (Giavini et al. 1983; Sparschu et al. 1971a), mice (Neubert and Dillman 1972; Smith et al. 1976), and rabbits (Giavini et al. 1982) following acute oral exposure to 2,3,7,8-TCDD. A single intraperitoneal injection of 2,3,7,8-TCDD (100 μg/kg) given between Gd 2–6 caused a high incidence of resorptions in C57BL/6J mice (Pratt et al. 1984). Similarly, increased resorptions were reported in rats exposed to mixed HxCDD during gestation, but not in those exposed to 2,7-DCDD or OCDD (Schwetz et al. 1973). In addition, abortions were observed in monkeys exposed to 2,3,7,8-TCDD for 3 weeks by gavage (McNulty 1984), and reduced reproduction was observed in those exposed chronically in the feed (Bowman et al. 1989b; Hong et al. 1989; Schantz et al. 1992). Finally, significantly decreased fertility in F1 and F2 generations was reported in a 3-generation reproductive study in rats exposed to 2,3,7,8-TCDD (Murray et al. 1979).

Investigations into the mechanism of CDD-induced decreased fertility revealed blocked estrous cycle in female mice exposed orally to 2,3,7,8-TCDD for an intermediate duration (Umbreit et al. 1987) and dose dependent decreases in uterine and hepatic cytosolic, and nuclear estrogen and progesterone receptor levels in rats after intraperitoneal 2,3,7,8-TCDD injection (Romkes and Safe 1988). Furthermore, 2,3,7,8-TCDD antagonized the estradiol-mediated increases in these levels. In addition, a dose-related reduction of uterine peroxidase activity and decreased uterine wet weight were seen after a single 2,3,7,8-TCDD injection in rats (Astroff and Safe 1990). 2,3,7,8-TCDD application also antagonized the treatment with estradiol. The authors concluded that 2,3,7,8-TCDD antagonized the estrogen-induced uterine response and that the Ah

receptor was involved in mediating the reaction. Other authors suggest that the anti-estrogen effect is mediated by 2,3,7,8-TCDD-induced metabolism of estrogens (Gierthy et al. 1987).

In non-pregnant female rats, decreases in ovarian weight, estrous cyclicity, ovulation rate, and the number of ova released were observed following a single dose of 2,3,7,8-TCDD (Li et al. 1995a, 1995b). Increases in LH and follicle stimulating hormone levels were also observed. The mechanisms involved in effects are thought to involve direct effects on the ovaries and effects on the hypothalamus/pituitary axis. The normal preovulatory surge of LH was not observed in the 2,3,7,8-TCDD-exposed rats, suggesting that 2,3,7,8-TCDD inhibited the positive feedback action of 17β-estradiol at the hypothalamic-pituitary axis (Li et al. 1995a). In hypophysectomized rats, 2,3,7,8-TCDD exposure resulted in a reduction of ovulation; Li et al. (1995a) suggests that this may be the result of a direct effect on the ovary, although the mechanism has not been elucidated. Endometriosis has been observed in monkeys chronically exposed to 2,3,7,8-TCDD in the diet (Rier et al. 1993). A possible association between 2,3,7,8-TCDD and endometriosis is supported by rat and mouse studies using surgically induced models of endometriosis (Cummings et al. 1996; Johnson et al. 1997). In contrast, Foster et al. (1997) found that 2,3,7,8-TCDD exposure diminished endometrial tissue growth in mice. These studies used different models of surgically induced endometriosis and highlight the complexity of the disease. In the Cummings et al. (1996) and Johnson et al. (1997) studies, the animals were exposed to 2,3,7,8-TCDD prior to the development of endometriosis, and immune suppression probably facilitated the growth of endometrial

tissue. In the Foster et al. (1997) model, 2,3,7,8-TCDD was administered after endometriosis development and 2,3,7,8-TCDD, via its anti-estrogenic effects, inhibited tissue growth. The relationship between CDD exposure and endometriosis in humans has not been adequately studied. In humans, the etiology of endometriosis likely involves a complex interplay between a number of diverse physiological factors including altered cell-mediated immunity and increased levels of growth hormone.

Although the human data regarding reproductive effects are inconsistent, a number of reproductive effects have been observed in animals, including decreased fertility, altered hormone levels, and gonad damage in males and females. The similarity between some of the effects observed in humans and animals suggest that reproductive effects may also occur in humans.

Developmental Effects. The developmental toxicity of 2,3,7,8-TCDD has been investigated in several human populations, with conflicting results. Most studies did not find increases in the number of birth defects in the children of men exposed to 2,3,7,8-TCDD in a chlorophenols manufacturing facility (Townsend et al. 1982) or during the Vietnam war (Aschengrau and Monson 1990; Erickson et al. 1984; Wolfe et al. 1995); or the children of parents living in Seveso, Italy (Bisanti et al. 1980; Mastroiacovo et al. 1988). Some studies did find increases in the incidence of specific defects (e.g., talipes, ventricular septal defect) in the infants of exposed fathers or mothers and fathers (Aschengrau and Monson 1990; Erickson et al. 1984; Hanify et al. 1981; Wolfe et al. 1995), but there was little consistency regarding the type of defect or the target

organ/system. The lack of exposure data, small sample sizes, and the lack of reliable data for birth defect rates prior to 2,3,7,8-TCDD exposure precludes drawing conclusions from these human studies. A section below summarizes information on health effects in humans associated with exposure to CDDs *in utero* and/or via breast milk. Developmental toxicity has been observed in rats, mice, rabbits, hamsters, and monkeys exposed to 2,3,7,8-TCDD and other CDD congeners. Perinatal exposure to 2,3,7,8-TCDD results in structural malformations, functional alterations, decreased growth, and fetal/newborn mortality. Many of the effects occurred at 2,3,7,8-TCDD doses which were not maternally toxic. Acute oral exposure to 2,3,7,8-TCDD during gestation caused an increased incidence of cleft palate and skeletal anomalies in offspring of rats (Giaviani et al. 1983; Huuskonen et al. 1994), mice (Abbott and Birnbaum 1989a; Courtney 1976; Dasenbrock et al. 1992; Neubert and Dillman 1972; Smith et al. 1976; Weber et al. 1985), and rabbits (Giavini et al. 1983). These effects were also observed in fetuses of mice that received subcutaneous injections of 2,3,7,8-TCDD during gestation (Courtney 1976; Poland and Glover 1980). The 2,3,7,8-TCDD-induced cleft palate is caused by the failure of the opposing palatal shelves to fuse (Pratt et al. 1984); 2,3,7,8-TCDD does not alter the size of the palatal shelves or interfere with the opposing shelves coming into contact. Under normal conditions, there is a cessation of medial cell proliferation, a degeneration of peridermal medial cells, and a transformation of basal cells to mesenchymal cells as the opposing palatal shelves come into contact and fuse (Abbott and Birnbaum 1989b). 2,3,7,8-TCDD exposure alters medial cell proliferation and differentiation resulting in the formation of stratified squamous epithelium. Abbott and Birnbaum (1990a) suggest that the altered proliferation and differentiation of the medial

cells is due to 2,3,7,8-TCDD-induced reductions of several growth factors (EGF, TGF-α, and TGF-β1) and increases in EGF receptor expression. EGF and TGF-α (which both bind to the EGF receptor) stimulate epithelial proliferation and differentiation and TGF-β1 inhibits epithelial proliferation. The increased levels of EGF receptor appear to compensate for the decreased EGF and TGF- α levels resulting in continued proliferation. Abbott et al. (1994a, 1994b) suggest that the altered expression of growth factors may be mediated by the Ah receptor. Exposure to 2,3,7,8-TCDD resulted in a dose-dependent down regulation of the Ah receptor throughout the palate; this probably occurs at the transcriptional level as decreases in mRNA were also observed (Abbott et al. 1994b). There is no evidence for direct Ah regulation of growth factors; rather, transcriptional regulation of related genetic activity may indirectly influence growth factor expression. Data which support an association between Ah receptor and cleft palate include a correlation between 2,3,7,8-TCDD binding to the Ah receptor and altered growth factor expression (Abbott et al. 1994b); finding of 2,3,7,8-TCDD-induced altered Ah receptor expression and altered growth factor expression at doses which do not induce cleft palate (Abbott et al. 1994b); and the inability of 2,3,7,8-TCDD to induce cleft palate in strains of mice which have low affinity for Ah receptors (Pratt et al. 1984; Silkworth et al. 1989b). Kidney malformations, particularly hydronephrosis, were observed in the offspring of rats (Giavini et al. 1983; Huuskonen et al. 1994), mice (Abbott et al. 1987a, 1987b; Courtney 1976; Moore et al. 1973; Silkworth et al. 1989b), and hamsters (Gray et al. 1995) orally exposed to 2,3,7,8-TCDD during gestation. Kidney defects were also observed in mouse offspring following *in utero* subcutaneous exposure to 2,3,7,8-TCDD (Courtney 1976) and in mice postnatally exposed to 2,3,7,8-TCDD via contaminated

mothers' milk (Couture-Haws et al. 1991b). The hydronephrosis observed in these offspring is the result of occlusion of the ureter and subsequent accumulation of urine in the kidney (Abbott et al. 1987a). Prenatal exposure to 2,3,7,8-TCDD results in hyperplasia of the epithelium in the ureter, obstruction of the ureteric lumen, and a restriction of the flow of urine. Abbott and Birnbaum (1990b) found that 2,3,7,8-TCDD interfered with the normal decline in EGF receptors in the ureteric epithelia, resulting in excessive proliferation. In the bladder, 2,3,7,8-TCDD exposure also resulted in an increase in the epithelial thickness and continued expression of EGF receptors. 2,3,7,8-TCDD also appears to directly damage the kidney. Under normal conditions, there is an increase in laminin and type IV collagen levels and a thickening of the *lamina densa* of the glomerular basement membrane, which is important in establishing the filtration barrier. Following exposure to 2,3,7,8-TCDD, there is a decreased expression of laminin and type IV collagen and a diminished thickening of the lamina densa (Abbott et al. 1987b). This immature filtration barrier is likely to result in proteinuria and may result in increased urine volume.

A number of recently published studies have shown that the developing reproductive system is very sensitive to the toxicity of 2,3,7,8-TCDD. In female rats, exposure to 2,3,7,8-TCDD on Gd 8 caused functional reproductive toxicity (accelerated onset of constant estrus, shortened reproductive lifespan, reduced ovarian weight, and cystic hyperplasia of the endometrium (Gray and Ostby 1995). Although there were no effects on fertility or estrous cyclicity when 2,3,7,8-TCDD exposure occurred after organogenesis (exposure on Gd 15) (Gray and Ostby 1995), external urogenital

malformations (clefting, hypospadias, vaginal thread, and delayed vaginal opening) were observed (Flaws et al. 1997; Gray and Ostby 1995; Gray et al. 1997a; Heimler et al. 1998). These malformations to external genitalia are likely to interfere with mating (Gray and Ostby 1995). The authors note that the effects on the external genitalia are similar to effects observed in animals exposed to potent estrogen-like chemicals (e.g., DES, estradiol), although it likely that these effects occur by a different mechanism. In male rats, perinatal exposure to 2,3,7,8-TCDD resulted in alterations in androgen status (decreased plasma testosterone levels, delay in testes descent, delay in external signs of puberty, and decreased ventral prostate and seminal vesicle weights), testes and cauda epididymis weights, and spermatogenesis (decreased daily sperm production, amount of mature sperm in cauda epididymis, and amount of sperm ejaculated), and in demasculinization and partial feminization of sexual behavior following exposure on Gd 15 (Bjerke and Peterson 1994; Bjerke et al. 1994a, 1994b; Gray et al. 1995; 1997b; Mably et al. 1992a, 1992b, 1992c; Sommer et al. 1996). In most of these studies, the experimental protocol involved gavaging the dams with a single dose of 2,3,7,8-TCDD on Gd 8 (Gray et al. 1995) or 15 (Bjerke and Peterson 1994; Bjerke et al. 1994a, 1994b; Gray et al. 1995; Mably et al. 1992a, 1992b, 1992c) and assessing a number of indices of reproductive development and function in newborn, juvenile, prepubescent, post-pubescent, and mature male rats. Because 2,3,7,8-TCDD is lipophilic and has a relatively long half-life, a single dose on Gd 15 will result in transplacental exposure from Gd 15 to birth and exposure via contaminated milk. Bjerke and Peterson (1994) compared the reproductive effects of 2,3,7,8-TCDD in rats exposed *in utero* to the effects observed in rats exposed to 2,3,7,8-TCDD only during lactation. Both *in utero* and lactational

exposure resulted in decreased plasma testosterone level, decreased seminal vesicle and ventral prostate growth, and decreased epididymal sperm reserves. Exposure *in utero* only also resulted in decreased daily sperm production and delayed puberty; and exposure by lactation only resulted in partial feminization of sexual behavior. These data suggest that the timing of the 2,3,7,8-TCDD exposure is important. The mechanism by which 2,3,7,8-TCDD disrupts the development of the reproductive system and whether all of the reproductive effects have similar mechanisms is not known. Early investigators of the effects of 2,3,7,8-TCDD on sexual behavior suggested that perinatal exposure to 2,3,7,8-TCDD resulted in impaired sexual differentiation of the central nervous system (Mably et al. 1992b). The results of the Bjerke et al. (1994b) study suggest that the 2,3,7,8-TCDD-induced alterations in sexual behavior were not due to 2,3,7,8-TCDD acting as an estrogen antagonist or altering ER capacities of hypothalamic nuclei. The volume of the sexually dimorphic nucleus in the preoptic area of the hypothalamus (SDN-POA), which is dependent upon testosterone derived estradiol in the brain during perinatal development, was not altered in 2,3,7,8-TCDD-exposed rats. Additionally, the sexual differentiation of ER concentration in brain nuclei which exhibit sexual dimorphism (ventromedial nuclei, medial preoptic nuclei, bed nucleus of the stria terminalis, periventricular preoptic area nucleus, cortical and medial amygdala, and arcuate nucleus) were not affected by 2,3,7,8-TCDD. Thus, 2,3,7,8-TCDD effects did not parallel those of either estrogen or androgen antagonists. Gray et al. (1995) also support the theory that 2,3,7,8-TCDD does not interfere with testosterone- and estrogen-dependent central nervous system sexual differentiation. In their study, no alterations in mounting behavior were observed in male hamsters perinatally exposed to 2,3,7,8-TCDD (in hamsters,

masculinization of the central nervous system requires perinatal exposure to testosterone). Bjerke et al. (1994b) proposed that 2,3,7,8-TCDD may affect other systems, such as brain amine content or growth factor expression of function, which would indirectly impact sexual differentiation. Similarly, Gray et al. (1995) suggested that 2,3,7,8-TCDD-induced alterations in the growth factors and receptors involved in urogenital system cell differentiation and proliferation may result in alterations in morphological sexual differentiation. Bjerke et al. (1994a) also found that the 2,3,7,8-TCDD-induced inhibition of ventral prostate weight and protein content imprinting was not due to perinatal reductions in plasma androgen levels because no effect on imprinting of the seminal vesicle, penis, or pituitary were observed in the 2,3,7,8-TCDD-exposed rats. Using a treatment regime that consisted of administration of a loading subcutaneous dose of 2,3,7,8-TCDD to female rats prior to mating, followed by weekly maintenance subcutaneous doses during mating, pregnancy, and lactation, Faqi et al. (1998) reported that sperm parameters were the most susceptible end points in male offspring examined at puberty (70 days old) and adulthood (170 days old). Based on pharmacokinetic considerations, the authors estimated that the lowest effective dose was <0.8 ng/kg/day. The sperm parameters that were altered were sperm number from cauda epididymis, daily sperm production, sperm transit rate, and percent abnormal sperm (more so in adults than in pubertal rats). No significant and/or consistent effects were observed on litter size, sex ratio, body weights, developmental landmarks, weight of sex organs, and sexual behavior. Testosterone levels were significantly reduced at age 170 days but not at age 70 days. In spite of sperm alterations, all exposed males exhibited normal reproductive performance and successfully impregnated untreated female to produce viable fetuses.

Recent studies have also focused on the role of the Ah receptor in the 2,3,7,8-TCDD-induced alterations in the development of the male reproductive system. Roman et al. (1998a) recently demonstrated the presence of both the Ah receptor and the receptor nuclear translocator (Arnt) in the testis, epididymis, vas deferens, ventral and dorsolateral prostate, and seminal vesicles from adult Holtzman rats. Arnt was localized in all organs in a variety of cell types; subcellular localization varied across organs and cell types within these organs. Unfortunately, technical difficulties precluded the evaluation of the Ah receptor distribution in the various organs. The authors also showed that a single oral dose of 25 μg 2,3,7,8-TCDD/kg produced significant induction of CYP1A1 in the ventral and dorsolateral prostate. CYP1A1 expression was localized in the epithelial cells of the ventral and lateral lobes of the prostate. Less CYP1A1 induction was seen in selected epithelial cells from other tissues, and no induction was detected in the testis. Also, 2,3,7,8-TCDD had no effect on Arnt protein expression, but Ah receptor expression was significantly reduced in all organs examined. In another study from this series, Roman and Peterson (1998) found that, relative to controls, *in utero* exposure to 2,3,7,8-TCDD (1 μg/kg) transiently decreased the amount of several prostate-specific androgen-regulated mRNAs, all of which are markers of a differentiated ductal epithelium. This was in contrast with observations in adults, in which 2,3,7,8-TCDD induced CYP1A1 mRNA without altering the amount of prostate-specific, androgen-regulated mRNAs. These results suggested that the developing prostate can directly respond to *in utero* and lactational exposure to 2,3,7,8-TCDD, and that this exposure not only impairs prostate growth but also delays prostate luminal epithelial cell differentiation. In yet an additional study from this series, Roman et al. (1998b) reported that in the most severely affected

animals, 2,3,7,8-TCDD produced alterations in the histological arrangement of epithelial and stromal cells and in the spatial distribution of androgen receptor expression.

Other developmental effects that have been observed in animals include immunotoxicity (thymic atrophy, immunosuppression, and alterations in thymocyte phenotypes) (Fine et al. 1989; Gehrs et al. 1997a, 1997b; Håkansson et al. 1987; Huuskonen et al. 1994; Luster et al. 1980; Madsen and Larsen 1989; Thomas and Hinsdill 1979), decreased fetal and newborn body weight (Abbott et al. 1992; Bjerke et al. 1994a; Bjerke and Peterson 1994), fetal/newborn mortality or decreased survival (Bjerke et al. 1994a; Bjerke and Peterson 1994; Huuskonen et al. 1994; McNulty 1984; Murray et al. 1979; Nau et al. 1986), and altered social behavior (Schantz et al. 1992).

Developmental toxicity has also been observed in animals exposed to other CDDs. These effects include heart defects in rats exposed to 2,7-DCDD (Schwetz et al. 1973); decreased thymic weight in rats exposed to 1,2,3,7,8-PCDD (Madsen and Larsen 1989); subcutaneous edema, decreased fetal growth, delayed ossification, dilated renal pelvis, and cleft palate in rats exposed to HxCDD (Schwetz et al. 1973); and subcutaneous edema in rats exposed to OCDD (Schwetz et al. 1973).

The animal database provides strong evidence that developmental toxicity is a sensitive end point following 2,3,7,8-TCDD exposure. Structural malformations, functional alterations (including impaired development of reproductive system), decreased growth, and fetal/newborn mortality have been observed in several animal species. Limited

human data on the developmental toxicity of CDDs is available. Most of these studies examined the occurrence of birth defects in children of males exposed to 2,3,7,8-TCDD. Deficiencies in the human data preclude drawing firm conclusion on the potential of 2,3,7,8-TCDD to induce developmental effects in humans. However, the animal data suggest that 2,3,7,8-TCDD is a likely human developmental toxicant.

Appendix B – The following is a quote that contains information on the immunological effects of dioxins from the ATSDR Toxicological Profile on dioxins, Pages 161-165, (ATSDR 1998).

2.2.2.3 Immunological Effects. An effect of sublethal exposures (acute, intermediate-term, or chronic) to 2,3,7,8-TCDD common to all species studied is thymic atrophy. Depletion of lymphocytes results in suppression of T-cell immunity. The T-cell responses studied have included delayed hypersensitivity responses, rejection of skin allografts, and *in vitro* mutagen responses of lymphoid cells. T-cell immunotoxicity is probably the most sensitive end point. Effects on T-cells can occur at levels of exposure three orders of magnitude lower than the effects on thymus cellularity. B-lymphocytes are also affected by 2,3,7,8-TCDD, but higher exposure levels are necessary for suppression of humoral immunity. CDDs suppress resistance to different infectious agents by various mechanisms (see Section 2.4 for more detailed information). Acute ED50 values for thymic atrophy following a single dose of 2,3,7,8-TCDD were calculated as 26 μg/kg in Sprague-Dawley rats, 0.8 μg/kg in Hartley guinea pigs, 280 μg/kg in C57BL/6 mice, and 48 μg/kg in Syrian hamsters (Hanberg et al. 1989). A significant dose-related reduction in

absolute thymus weight was reported in young male Wistar rats administered single doses of 1 μg/kg 2,3,7,8-TCDD; this effect was paralleled by a significant decrease in thymic cellularity (De Heer et al. 1994b). Thymic atrophy was shown to be initiated in the thymus cortex on day 4 after a single dose of 25 μg/kg 2,3,7,8-TCDD (De Heer et al. 1994a). The initial lymphodepletion in the cortex was followed by a secondary depletion of medullary thymocytes on day 6, and on day 10, a preferential depletion of cortical thymocytes was no longer observed. Decreased thymus weight was reported in pregnant C57BL/6J mice exposed to 0.5 μg/kg/day 2,3,7,8-TCDD for 10 days (Silkworth et al. 1989b). Offspring of C57BL/6J mice similarly exposed to 1.5 μg/kg/day had severe thymic atrophy, cellular depletion and altered thymocyte antigen expression, and immune function (Holladay et al. 1991). In contrast, similar changes were observed in DBA/2J mice only after exposure to higher doses of 8 μg/kg/day. Furthermore, thymic atrophy was observed in rhesus monkeys after a single dose of 70 μg/kg (McConnell et al. 1978a) and in guinea pigs after a dose of 6 μg/kg (Umbreit et al. 1985).

Treatment of rats with daily doses of 0.72 μg 2,3,7,8-TCDD/kg/day by gavage for 14 days did not alter pontaneous NK-cell activity in the lung, but significantly suppressed influenza virus-augmented NK ctivity (Yang et al. 1994). A significantly higher virus titer was observed on days 2, 3, and 4 in whole lung homogenate from rats treated with a single dose of 10 μg/kg (Yang et al. 1994). Decreased resistance to infection, as evidenced by increased mortality, was observed in B6C3F1 mice infected with *Streptococcus pneumoniae* and administered 1 μg/kg/day 2,3,7,8-TCDD for 14 days (White et al. 1986), and in B6C3F1 mice infected with influenza A virus and

administered a single gavage dose of 0.01, 0.05, or 0.1 μg/kg 2,3,7,8-TCDD (Burleson et al. 1996). The Burleson et al. (1996) study identified a NOAEL of 0.005 μg/kg for this effect. Acute exposure to 2,3,7,8-TCDD reduced polymorphonuclear activity in B6C3F1 mice at 5 μg/kg (no effect was seen in DBA/2N mice) (Ackermann et al. 1989). Suppressed antibody response to sheep erythrocytes (SRBC) was reported in B6C3F1 mice that were given a single gavage dose of 1 μg/kg; no such effect was found after a single dose of 0.5 μg/kg (Holsapple et al. 1986a). However, suppression of the antibody response occurred after 14 daily doses of 0.1 μg/kg/day. In rats, a single dose of 20 μg 2,3,7,8-TCDD/kg administered 5 days before immunization significantly enhanced the primary antibody response to SRBC as judged by a significant increase in serum IgG levels 7 days after immunization (Fan et al. 1996). However, serum IgM levels were not significantly affected by doses of 2,3,7,8-TCDD of up to 40 μg/kg. Fan et al. (1996) also observed that cell-mediated immunity, tested with a delayed-type hypersensitivity (DTH) assay, exhibited a U-shaped response to treatment with 2,3,7,8-TCDD, as doses of 1–20 μg/kg increased the DTH response, whereas doses of 30–90 μg/kg decreased it, even below control levels.

Suppressed total serum complement activity was observed in female B6C3F1 mice exposed to a single gavage dose of 14 μg/kg or 14 daily doses of 0.01 μg/kg/day (White et al. 1986). Serum levels of complement component C3 were also suppressed at doses of $0.5 μg/kg 2,3,7,8-TCDD (White et al. 1986). Subsequent studies by the same group showed that the 2,3,7,8-TCDD-induced reduction in serum C3 is not the result of a decrease in C3 production by hepatocytes but, at least in part, may be due to increased

catabolism (Lin and White 1993). Single gavage doses of 2.5 μg 2,3,7,8-TCDD/kg suppressed cytotoxic T-lymphocyte (CTL) activity in mice challenged with a tumor allograft by a mechanism that did not involve elevation in plasma glucocorticoid levels (De Krey and Kerkvliet 1995). This was directly correlated with reduced numbers of splenic CTL effector cells (Kerkvliet et al. 1996). In these same animals, a suppression of the alloantibody response was correlated with a decreased expansion of the B-cell splenocyte population. This dose of 2,3,7,8-TCDD also initially induced interferon-γ, interleukin-2, and tumor necrosis factor production, but the normal increase of these in response to the tumor allograft was not observed. Based on these and additional studies, the authors concluded that these effects are due to TCDD initially interfering with the activation of CD4+ T cells and possibly T helper-B cell interactions. A recent study from the same group of investigators presented evidence that immune 2,3,7,8-TCDD-induced suppression in C57BL/6 mice is not caused by direct alterations in the production of immunomodulatory metabolites of arachidonic acid (Lawrence and Kerkvliet 1997). The above results indicate that immunological effects occur after moderate-to-low single doses or after repeated low doses that accumulate in the body, suggesting that the total dose of 2,3,7,8-TCDD is important. As shown in Figure 2-1, immunotoxicity was a very sensitive end point; the lowest LOAEL for immune effects is 0.01 μg/kg/day (Burleson et al. 1996; White et al. 1986). In the Burleson et al. (1996) study, decreased resistance to infection was observed in mice receiving a single gavage dose of 0.01 μg/kg, and no effects were observed at 0.005 μg/kg. Reduced serum complement levels were observed in mice exposed to 0.01 μg/kg/day for 14 days (White et al. 1986); no NOAEL was identified in this study. The NOAEL of 0.005 μg/kg/day identified in the Burleson et al.

(1996) study was used to derive an acute oral MRL for 2,3,7,8-TCDD of 2×10-4 μg/kg/day as described in the footnote to Table 2-2, Section 2-5, and in Appendix A.

Several immunological effects were observed following intermediate-duration exposure to 2,3,7,8-TCDD. Decreased thymus weight after 2,3,7,8-TCDD exposure was observed in rats dosed by gavage with 0.71 μg/kg/day for 6 weeks (Vos et al. 1973), in the F3 generation of rats receiving 0.01 μg/kg/day (Murray et al. 1979), and in guinea pigs receiving 0.005 μg/kg/day or 0.03 μg/kg/day (thymic atrophy) in the feed for 90 days (DeCaprio et al. 1986). A significant reduction in absolute and relative thymus weight was observed in male Sprague-Dawley rats administered 2,3,7,8-TCDD by gavage at doses equivalent to 0.8 μg/kg/day (only dose level tested) for 13 weeks (Viluksela et al. 1994). Spleen weight was not significantly altered. Similar results were reported in female Sprague-Dawley rats fed for 13 weeks a diet that supplied doses of $0.014 μg 2,3,7,8-TCDD/kg/day (Van Birgelen et al. 1995). Relative spleen weight was increased at $0.047 μg 2,3,7,8-TCDD/kg/day. Decreased cell-mediated immunity was found in mice and guinea pigs exposed by gavage to 0.71 μg/kg/day for 4 weeks and 0.03 μg/kg/day for 8 weeks, respectively (Vos et al. 1973). Guinea pigs seem to be especially sensitive to 2,3,7,8-TCDD toxicity; an intermediate-duration exposure to 0.001 μg/kg/day reduced the lymphocyte counts, and exposure to 0.03 μg/kg/day caused decreased humoral immunity and thymic atrophy (Vos et al. 1973). A recent study examined the effect of low-level dietary exposure to 2,3,7,8-TCDD to young adult male Leeds strain rats (Badesha et al. 1995). A 30-day exposure to approximately 0.1 μg/kg/day (or a total dose of approximately 3 μg/kg) resulted in an exposure duration-dependent reduction of *in*

vitro lipopolysaccharide- induced production of interleukin-1 in cultures of their splenic macrophages. A 180-day exposure to approximately 0.017 μg/kg/day suppressed the production of interleukin-2 by either concanavalin A or phorbol ester/calcium ionophore stimulation, and reduced the lectin-induced proliferation of splenic T cells. The authors concluded that exposure to a low dietary dose of 2,3,7,8-TCDD suppresses the functions of several T-cell subsets. The highest NOAEL value for immunological effects (decreased thymus weight) was 0.0007 μg/kg/day 2,3,7,8-TCDD given to the most sensitive species, guinea pigs, in the diet (DeCaprio et al. 1986). The NOAEL value of 0.0007 μg/kg/day was used to derive an intermediate-duration oral MRL for 2,3,7,8-TCDD of 2×10-5 μg/kg/day as described in the footnote to Table 2-2, Section 2.5, and in Appendix A.

Increased mortality that was indicative of altered immunity was also observed in C57BL/6Jfh mice challenged with *Salmonella bern* following exposure to 1 μg/kg/day of 2,3,7,8-TCDD by gavage once a week for 4 weeks (Thigpen et al. 1975); no significant effects were observed at 0.5 μg/kg/day. In the same study, using the same experimental design, doses of up to 20 μg/kg/day of 2,3,7,8-TCDD had no significant effect on mortality in mice infected with *Herpesvirus suis* (Thigpen et al. 1975). Exposure to 0.5 μg/kg/day 2,3,7,8-TCDD once a week for 5–8 weeks caused suppression of humoral activity in C57BL/6 mice (Vecchi et al. 1983a). In addition, lymph node atrophy was reported in monkeys exposed to a lethal dose of 0.011 μg/kg/day in the feed for 9 months (Allen et al. 1971). Administration of 2,3,7,8-TCDD at approximately 0.071 μg/kg/day to Osborne-Mendel rats or at about 0.3 μg/kg/day to B6C3F1 mice by gavage for 104 weeks

produced no histological alterations in the spleen or thymus (NTP 1982b). Chronic exposure to 2,3,7,8-TCDD in food induced thymic atrophy in Sprague- Dawley rats at 0.1 μg/kg/day in a 2-year study (Kociba et al. 1978a) with the highest NOAEL of 0.01 μg/kg/day.

Furthermore, rhesus monkeys exposed chronically to 0.002 μg/kg/day 2,3,7,8-TCDD in the feed exhibited degeneration of the bone marrow and lymphoid tissues (Hong et al. 1989). A recent study examined the effect of long-term exposure to 2,3,7,8-TCDD on various immune cell phenotypes of female C57 BL/6 mice (Oughton et al. 1995). The mice were administered 0.2 μg 2,3,7,8-TCDD/kg once per week for 14–15 months; this resulted in a cumulative dose of 12–13 μg/kg (approximately 0.03 μg/kg/day) and a concentration of 2,3,7,8-TCDD in adipose tissue of 1.27 ng/g abdominal fat. There were no significant 2,3,7,8-TCDD-related effects on thymus and spleen weight or in the cellularity of these tissues. Exposure to 2,3,7,8-TCDD induced subtle changes in thymic phenotypes which, according to the authors, were of questionable biological relevance given the age-related decrease in thymic cellularity observed. 2,3,7,8-TCDD did not alter the frequencies of the major leukocyte subpopulations, but significantly altered functionally discrete subpopulations within the T-cell compartment. The most notable change was a decrease in the frequency of memory T helper cells, with a concomitant increase in the proportion of naive T helper cells. Oughton et al. (1995) also presented preliminary data suggesting that phenotypic changes in spleen cells correlated with similar changes in blood cells.

Other CDD congeners also appear to affect the immune system. Significant dose-related decreases in absolute and relative thymus weight were observed in male Sprague-Dawley rats administered doses equivalent to 4–110 μg/kg/day 1,2,3,4,6,7,8-HpCDD for 13 weeks by gavage (Viluksela et al. 1994). A dose level of 0.3 μg/kg/day was without significant effect. Treatment with 1,2,3,4,6,7,8-HpCDD had no significant effect on spleen weight. Suppressed antibody response was reported in B6C3F1 mice after 2 weeks of exposure to 0.1 μg/kg/day of 2,7-DCDD, but not after exposure to 10 μg/kg/day of OCDD (Holsapple et al. 1986b). Depressed antibody response was found in C57BL/6 mice exposed to a single dose of 33 μg/kg/day 1,2,3,4,6,7,8-HpCDD (Kerkvliet and Brauner 1987). Suppressed serum complement activity was found in B6C3F1 mice following 2 weeks of exposure to 1 μg/kg/day 1,2,3,6,7,8-HxCDD (White et al. 1986). Splenic hyperplasia was observed in Osborne-Mendel rats after exposure to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD at 7.1 μg/kg/day, 1 day/week for 13 weeks (NCI/NTP 1980).

In conclusion, the immunological system was a sensitive target of CDD toxicity under experimental conditions in animals. Effects on all types of mediated immunity were seen at doses of 2,3,7,8-TCDD as low as 0.01 μg/kg. Doses of 2,3,7,8-TCDD that were well below the lethal dose affect humoral immunity. Thymic atrophy occurs as single or multiple doses approach those that may increase lethality. Neonates and young animals are much more sensitive than adults to most of the immunological responses. The highest NOAEL values and all reliable LOAEL values for immunological effects in each species

and duration category for each congener are recorded in Table 2-2 and 2-3 and plotted in Figures 2-1 and 2-2.

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